Outcome of Elderly Patients with Diffuse Large B-cell Lymphoma Treated with R-CHOP: Results from the UK NCRI R-CHOP14v21 trial with combined analysis of molecular characteristics with the DSHNHL RICOVER-60 trial

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Abstract

Background: There is an on-going debate whether 2- or 3-weekly administration of R-CHOP is the preferred first-line treatment for elderly patients with diffuse large B-cell lymphoma (DLBCL). The UK NCRI R-CHOP14v21 randomized phase 3 trial did not demonstrate a difference in outcomes between R-CHOP-14 and R-CHOP-21 in newly diagnosed DLBCL patients aged 19-88 years, but data on elderly patients have not been reported in detail so far. Here, we provide a subgroup analysis of patients ≥60 years treated on the R-CHOP14v21 trial with extended follow-up.

Patients and Methods: 604 R-CHOP14v21 patients ≥60 years were included in this subgroup analysis, with a median follow-up of 77.7 months. To assess the impact of *MYC* rearrangements (*MYC*-R) and double-hit-lymphoma (DHL) on outcome in elderly patients, we performed a joint analysis of cases with available molecular data from the R-CHOP14v21 (*N*=217) and RICOVER-60 (*N*=204) trials.

Results: Elderly DLBCL patients received high dose intensities with median total doses of ≥98% for all agents. Toxicities were similar in both arms with the exception of more grade ≥3 neutropenia (*P*<0.0001) and fewer grade ≥3 thrombocytopenia (*P*=0.05) in R-CHOP-21 vs. R-CHOP-14. The elderly patient population had a favorable 5-year overall survival (OS) of 69% (95%CI: 65-73). We did not identify any subgroup of patients that showed differential response to either regimen. In multivariable analysis including individual factors of the IPI, gender, bulk, B2M and albumin levels, only age and B2M were of independent prognostic significance for OS. Molecular analyses demonstrated a significant impact of *MYC*-R (HR=1.96; 95%CI: 1.22-3.16; *P*=0.01) and DHL (HR=2.21; 95%CI: 1.18-4.11; *P*=0.01) on OS in the combined trial cohorts, independent of other prognostic factors.

Conclusions: Our data support equivalence of both R-CHOP application forms in elderly DLBCL patients. Elderly *MYC*-R and DHL patients have inferior prognosis and should be considered for alternative treatment approaches.

Trial numbers: ISCRTN 16017947 (R-CHOP14v21); NCT00052936 (RICOVER-60)

Key words

Diffuse large B-cell lymphoma, elderly, R-CHOP, MYC, double-hit lymphoma

Key message

We provide a detailed outcome analysis of elderly patients with DLBCL treated with 2- or 3-weekly R-CHOP within the UK R-CHOP14v21 trial, indicating equivalence of both regimens in the elderly patient population. In a joint analysis of R-CHOP14v21 and RICOVER-60 molecular data, we demonstrate that MYC rearrangements and double-hit-lymphoma are independent poor prognostic factors in elderly DLBCL.

Introduction

Elderly patients with diffuse large B-cell lymphoma (DLBCL) have a worse prognosis compared to the younger patient population. This is partly explained by lower treatment tolerability in elderly patients with difficulties to administer adequate doses of chemotherapy. However, even when receiving comparable treatment intensities, elderly DLBCL patients have inferior outcome, potentially indicating more aggressive disease biology. Therefore, dose-intensified administration of R-CHOP immuno-chemotherapy might be of particular benefit for elderly DLBCL patients to overcome these high-risk factors. Treatment of patients >60 years (y) with 6x R-CHOP-14 plus 2x rituximab in the German RICOVER-60 trial has achieved the best long-term outcome in elderly DLBCL patients published to date.[1] However, superiority of dose-intensified R-CHOP-14 compared to the 3-weekly administration in elderly DLBCL patients could not be demonstrated in randomized trials.

The GELA LNH03-6B trial comparing R-CHOP-14 and R-CHOP-21 in DLBCL patients aged 60-80y showed no difference of either regimen,[2] but results were criticized due to high treatment-related mortality and low dose intensities in the R-CHOP-14 arm. The UK NCRI R-CHOP14v21 trial compared the 2- and 3-weekly R-CHOP regimens in DLBCL patients aged 18-88y and similarly did not observe a difference in outcome across age groups.[3] However, outcomes of the elderly R-CHOP14v21 trial cohort have not been reported separately and it remained unclear whether particular subgroups of elderly patients benefit from intensified treatment.

The International Prognostic Index (IPI) is widely used for prognostication of younger and elderly DLBCL patients. Due to differences in disease biology and outcomes it has been proposed to use separate prognostic scores for the elderly patient group,[4,5] but these have not yet been validated in large independent cohorts.

Several molecular high-risk markers have been identified in DLBCL that could potentially refine clinical prognostic models. Cell-of-origin (COO) assessment of DLBCL according to gene-expression-profiling separates the germinal center B-cell (GCB) and the poor prognostic activated B-cell (ABC) subtypes, but these analyses lack prospective validation and methodological problems currently limit their use in standard practice. The negative prognostic impact of *MYC* rearrangements (*MYC*-R) as well as *MYC*- and concomitant *BCL2*- or *BCL6* rearrangements (double-hit lymphoma; DHL) has been shown in several DLBCL cohorts.[6,7] The prognostic significance of *MYC*-R seems to be particularly high in older DLBCL patients.[6] Due to the low incidence of *MYC*-R and DHL and possibly due to their age-dependent relevance, an independent prognostic significance of these markers in

multivariate models has not yet been demonstrated in prospective trial cohorts of R-CHOP-treated patients.

The aim of this subgroup analysis was to provide detailed outcomes and toxicity data on elderly patients treated within the R-CHOP14v21 trial and to investigate the impact of clinical and molecular factors on outcome in this age group.

Patients and Methods

Patient characteristics in the R-CHOP14v21 trial have been published in detail.[3] A brief description of the trial is given in the Supplement (available at *Annals of Oncology* online).

Of 1080 R-CHOP14v21 patients, 604 were ≥60y and included in the current analysis. Details of statistical analyses are provided in the Supplement.

COO was assessed by the immunohistochemistry (IHC)-based Hans algorithm. Assessment of *MYC*-, *BCL2*- and *BCL6*-rearrangements was done with fluorescence in-situ hybridization (FISH; *N*=217). DHL was defined as presence of *MYC*- and either *BCL2*- or *BCL6*-rearrangements. In order to increase the sample size to assess the impact of *MYC*-R and DHL on outcome in elderly DLBCL patients, we performed a joint analysis with data from 204 elderly DLBCL patients treated on the RICOVER-60 trial who had molecular results available (Table S1). Details of the German high-grade non-Hodgkin lymphoma study group (DSHNHL) RICOVER-60 trial and methods of molecular analyses within the trial have been previously described.[1,7]

Results

We included 604 elderly patients from the R-CHOP14v21 trial in this subgroup analysis. Patients' median age was 67y (range 60-88). Baseline characteristics were well balanced between treatment arms (Table 1). There was a trend towards a higher rate of *BCL6* rearrangements and DHL in R-CHOP-14 (*P*=0.10 and *P*=0.06, respectively).

Dose intensities were high in both trial arms. Median total doses of cyclosphosphamide, doxorubicin, vincristine, prednisolone and rituximab received were 98% vs. 99%, 98% vs. 99%, 100% vs. 100%, 98% vs. 100%, and 98% vs. 98% in R-CHOP-21 and R-CHOP-14, respectively. Seventy one (24%) patients on R-CHOP-21 and 46 (15%) patients on R-CHOP-14 did not complete all treatment cycles (*P*=0.01). Reasons for early treatment termination are listed in Table S2, with treatment-related toxicity being the most common cause. Frequency of dose reductions was similar in both arms (15% for R-CHOP-21 vs. 16% for R-CHOP-14; *P*=0.73).

Treatment toxicities are given in Table 2. There was evidence of more grade ≥3 neutropenia (62% vs. 36%; *P*<0.0001) and less grade ≥3 thrombocytopenia (7% vs. 12%; *P*=0.05) in R-CHOP-21 compared to R-CHOP-14. Patients on R-CHOP-21 had lower incidence of anemia (20% vs. 31%; *P*=0.001), with a similar trend for grade ≥3 anemia (2% vs. 5%; *P*=0.11). No significant difference in the incidence of fever and infections or any other toxicity was observed. The incidence of treatment-related deaths, fatal cardiac events and secondary malignancies were similar in both arms (Table S3).

Response was assessable in 274 patients in each arm. There was no evidence of a difference in response rates between R-CHOP-21 and R-CHOP-14 [complete response (CR)/unconfirmed CR (CRu): 67% vs. 62%, *P*=0.21; overall response rate (ORR) both 91%; Table 3]. CR/CRu rates after 4 cycles of therapy were 39% and 33%, respectively (*P*=0.15). 61% and 60% of patients are still alive without progression (Table S3). Four patients on R-CHOP-21 and seven on R-CHOP-14 presented with central nervous system relapse (*P*=0.55).

After a median follow-up of 77.7 months, there was no evidence of a difference in progression-free survival (PFS) and overall survival (OS) between treatment arms in patients ≥60y or ≥70y (Figure 1A/B). No difference in survival between R-CHOP-21 and R-CHOP-14 was observed in patients who only achieved partial response (PR) after 4 cycles (*P*=0.79 for PFS; *P*=0.68 for OS). There was also no difference between treatment arms with respect to gender (*P*=0.54 for PFS; *P*=0.67 for OS) or IPI (*P*=0.64 for PFS; *P*=0.50 for OS). 5y-PFS was 64% (95%CI: 60-68) in patients ≥60y and 58% (95%CI: 51-65) in patients ≥70y. 5y-OS was 69% (95%CI: 66-73) and 61% (95%CI: 54-68), respectively.

63/280 (23%) patients with available data received consolidation radiotherapy. Of those, 36 had initial bulk, 20 extranodal disease, and 10 had both. Disease status before radiotherapy was available for 61 patients: 23 (37%) CR/CRu, 31 (51%) PR, 7 (12%) SD. In patients with PR or SD who are supposed to benefit most from radiotherapy, the use of radiotherapy was not associated with OS (Figure S3).

In multivariable analysis, only age and B2M levels were of independent prognostic significance for OS (Table S4). There was no significant impact of COO subtypes on outcomes (Figure S1). When comparing prognostic scores IPI, R-IPI, E-IPI and ABE4 (Table S5; Figure S2), ABE4 achieved the best fit and discrimination for predicting OS, followed by the IPI. Similar results were obtained for PFS (data not shown).

To assess the impact of *MYC*-R and DHL on outcome we performed a joint analysis with cases from RICOVER-60. 23/217 (11%) patients from our cohort and 19/204 (9%) patients from RICOVER-60 had *MYC*-R as determined by FISH. 14/215 (7%) and 9/182 (5%) had DHL, respectively. *MYC*-R and DHL cases had significantly worse OS compared to cases without these abnormalities [HR=1.96 (95%CI: 1.22-3.16); *P*=0.01 and HR=2.21 (95%CI: 1.18-4.11); *P*=0.01, respectively); Figure 2]. Similar effect sizes were observed after adjusting for individual IPI factors and trial arms [HR=1.76 (95%CI: 1.09-2.85); *P*=0.02 and HR 2.08 (95%CI: 1.11-3.90); *P*=0.02, respectively)]. The difference in OS between DHL and *MYC*-R was not significant (HR=1.38 (95%CI: 0.55-3.43; *P*=0.49). There was no significant impact of *BCL2*- or *BCL6*-rearrangements on OS (*P*=0.34 and *P*=0.99, respectively).

Discussion

With a median follow-up of 6.5y, we provide a detailed analysis of outcome and toxicities from patients with newly diagnosed DLBCL aged ≥60y treated on the phase 3 R-CHOP14v21 trial.

Elderly DLBCL patients in our cohort had an excellent long-term outcome with 5y-OS of 69% (3y-PFS 71%; 3y-OS 76%). These results are similar to data from elderly DLBCL patients treated with 6x R-CHOP-14 on RICOVER-60 (3y-PFS 73%; 3y-OS 78%) and better than outcomes in the GELA LNH03-6B trial (3y-PFS 61%; 3y-OS 73%).[1,2] Of note, patients' median age was higher in LNH03-6B (70y) compared to our cohort (67y) and RICOVER-60 (68y). In addition, there were more cases presenting with high IPI (3-5) in the LNH03-6B trial (75% vs. 57% in our subgroup vs. 43% in RICOVER-60), which might have contributed to inferior outcome seen in this trial population.

Toxicity profiles in our cohort of elderly DLBCL patients were favorable in both treatment arms. As expected, patients on R-CHOP-21 had a higher incidence of neutropenia probably due to reduced use of G-CSF, but less thrombocytopenia. Importantly, there was no difference in infectious complications or treatment-related deaths. The incidence of deaths during chemotherapy was very low at 1.7%, suggesting adequate management of elderly patients in participating centers. In the LNH03-6B trial, a high treatment-related mortality of 9% was observed in the initial recruitment period, which improved towards the end of the study, indicating gain of clinical experience with dose-intensified treatment in elderly patients. With 6.5y median follow-up, there was no difference in long-term toxicity, specifically cardiac events and secondary malignancies, between arms.

Dose intensities were high in both arms and as seen in the entire R-CHOP14v21 trial cohort.[3] The low dose intensity of 88% for R-CHOP-14 in the LNH03-6B trial could have potentially underestimated efficacy of the 2-weekly regimen. Our results support equivalence of both regimens in elderly DLBCL patients when adequate doses are achieved. However, the study was not powered for this post-hoc subgroup analysis in elderly patients.

We did not identify any subgroup of elderly DLBCL patients that showed differential response to either regimen, including gender and IPI groups. No difference between treatment arms could be seen in patients ≥70y. An analysis of patients ≥80y was not feasible due to low numbers (*N*=20). Moreover, there was no benefit of dose-intense treatment in late responders who had not achieved CR/Cru after 4 cycles.

Consolidation radiotherapy was at the discretion of the investigators and performed in 23% of elderly patients with available data. The main indication for radiotherapy was initial bulky or

extranodal disease. The benefit of radiotherapy to initial bulk in elderly DLBCL patients is reported to be greatest for patients who are not in CR/CRu after induction therapy.[8] Accordingly, most patients in our analysis received radiotherapy to PR or SD at the end of treatment, without evidence of a survival benefit for this strategy. However, these data have significant limitations (non-randomized approach, small numbers). In addition, no PET-CT data were recorded. The on-going DSHNHL OPTIMAL>60 trial will investigate whether consolidation radiotherapy can be safely omitted in elderly DLBCL patients who are PET-negative at the end of treatment.

Remarkably, PFS of elderly patients was only 8 percentage points worse at 5y compared to younger patients (5y-PFS 64% vs. 72%), supporting the concept of treating elderly patients with full doses of chemotherapy whenever possible. Toxicities were also similar between elderly and younger patients (data not shown), besides a significantly higher rate of grade ≥3 neutropenia in elderly ($P \leq 0.001$).

Differences between DLBCL of elderly and younger patients have been described on the molecular level, with higher frequencies of ABC subtypes, *BCL6* rearrangements, gains in 1q21, 18q21, and 7q21, and a higher genetic complexity associated with increasing age.[9] We did not observe material differences in the frequency of *MYC*-R, *BCL6*- and *BCL2*-rearrangements between age groups, nor in the incidence of IHC-based cell-of-origin subtypes (data not shown). We found lower frequency of bulky disease and higher B2M levels in elderly compared to younger patients, implying differences in disease biology between both groups.

Age-specific clinical and molecular features suggest the need for a separate prognostic scoring system for elderly patients. We compared performances of two recently proposed prognostic scores for elderly DLBCL (ABE4[5] and E-IPI[4]) with the standard IPI and R-IPI in our cohort. Both scores use an age cut-off of 70y. ABE4 further incorporates bulky disease and separates PS≥1 instead of ≥2. The ABE4 performed best in our cohort, despite bulky disease not being significantly associated with patient outcomes. Therefore, separating patients with PS 0 from those with PS≥1 could be a more appropriate cut-off in an elderly patient group. Both ABE4 and IPI distinguished meaningful prognostic groups for PFS and OS. However, clinical utility of the ABE4 score might be limited by the fact that only 9% of patients from our cohort were in the high-risk group compared to 14% in the original Czech Lymphoma Registry.[5] As discussed by Ziepert *et al.*,[10] introduction of new scores have to be seen with caution and should only be considered if properly validated and if changing patients' management. The main use of the IPI has been in the context of clinical trials, allowing risk-stratification of patients and facilitating comparison of results across trials. A NCCN-IPI has recently been proposed which separates three different age groups as risk

factors.[11] The great disadvantage of this score is that it cannot be used for elderly and young patient groups separately and is therefore unsuitable for age-specific DLBCL trials. In contrast, the IPI as age-adjusted IPI has been validated in both young and elderly DLBCL.

In line with previous findings, IHC-based cell-of-origin classification did not impact on outcomes, further underscoring limitations of this method. However, final analyses of the REMoDL-B trial will reveal if the concept of cell-of-origin classification as prognostic marker holds true when assessed prospectively.[12] Our combined analysis of FISH data from R-CHOP14v21 and RICOVER-60 demonstrates for the first time independent prognostic significance of both *MYC*-R and DHL in patients treated with R-CHOP within prospective cohorts. A negative prognostic impact of *MYC*-R and DHL has been reported in several heterogeneous DLBCL populations, but did not reach independent significance in trial cohorts due to small numbers.[3,7] On-going prospective trials will reveal if these patients benefit from upfront treatment intensification.

In conclusion, our data demonstrate excellent short and long-term results with both R-CHOP-14 and R-CHOP-21 in elderly DLBCL patients. This analysis contributes important information to the longstanding discussion about optimal management of the elderly DLBCL patient population and provides a detailed analysis of molecular and clinical prognostic factors in this age group.

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Disclosure

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Tables and Figures

Table 1: Baseline characteristics

Characteristics	R-CHOP-21 (*N*=301) *n* (%)	R-CHOP-14 (*N*=303) *n* (%)
Age (years)		
60-69	192 (64%)	196 (65%)
≥70	109 (36%)	107 (35%)
Sex		
Female	148 (49%)	150 (50%)
Male	153 (51%)	153 (50%)
WHO performance status		
0	120 (40%)	143 (47%)
1	132 (44%)	118 (39%)
2	49 (16%)	42 (14%)
Stage (*N*=596)		
IA	9 (3%)	9 (3%)
IB	6 (2%)	7 (2%)
II	90 (30%)	83 (28%)
III	91 (31%)	104 (35%)
IV	102 (34%)	95 (32%)
Bulk (*N*=601)	139 (47%)	126 (42%)
B symptoms	121 (40%)	134 (44%)
Elevated LDH	200 (66%)	197 (65%)
>1 extranodal sites	94 (31%)	82 (27%)
IPI score		
1	48 (16%)	44 (15%)
2	75 (25%)	90 (30%)
3	98 (33%)	104 (34%)
4	66 (22%)	56 (18%)
5	14 (5%)	9 (3%)
Subtype (*N*=317)		
GCB	76 (50%)	82 (50%)
non-GCB	77 (50%)	82 (50%)
β2-microglobulin ≥3mg/L (*N*=371)	88 (51%)	102 (52%)
Albumin ≤35g/L (*N*=598)	100 (34%)	86 (29%)
MYC rearrangement (*N*=217)	9 (9%)	14 (12%)
BCL2 translocation (*N*=220)	26 (25%)	33 (28%)
BCL6 rearrangement (*N*=218)	17 (16%)	30 (26%)
Double-hit abnormality (*N*=215)	5 (5%)	9 (8%)

Table 2: Most common grade ≥3 toxicities and cause of treatment-related deaths

	R-CHOP-21 (*N*=301)		R-CHOP-14 (*N*=303)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
All toxicities	292 (97%)	216 (72%)	299 (99%)	182 (60%)
Neutropenia	224 (74%)	185 (61%)	138 (46%)	109 (36%)
Thrombocytopenia	73 (24%)	22 (7%)	112 (37%)	37 (12%)
Anemia	60 (20%)	6 (2%)	95 (31%)	14 (5%)
Infection	145 (48%)	71 (24%)	146 (48%)	71 (23%)
Fever	70 (23%)	16 (5%)	56 (18%)	16 (5%)
Mucositis	143 (48%)	4 (1%)	167 (55%)	8 (3%)
Nausea	188 (62%)	7 (2%)	151 (50%)	12 (4%)
Vomiting	98 (33%)	7 (2%)	82 (27%)	9 (3%)
Diarrhoea	109 (36%)	12 (4%)	113 (37%)	16 (5%)
Constipation	185 (61%)	7 (2%)	160 (53%)	8 (3%)
Neurological	167 (55%)	23 (8%)	183 (60%)	36 (12%)
Fatigue	240 (80%)	31 (10%)	252 (83%)	40 (13%)
Bone pain	68 (23%)	7 (2%)	102 (34%)	6 (2%)
Cardiac	29 (10%)	2 (1%)	29 (10%)	9 (3%)

Treatment-related deaths:

3 in R-CHOP-21: 2 non-neutropenic sepsis, 1 neutropenic sepsis

7 in R-CHOP-14: 2 non-neutropenic sepsis, 1 neutropenic sepsis, 1 renal failure, 3 not specified

Table 3: Response to treatment

End of treatment response	R-CHOP-21 (*N*=274) *n* (%)	R-CHOP-14 (*N*=274) *n* (%)
Complete response (CR)	145 (53%)	119 (43%)
Unconfirmed complete response (CRu)	39 (14%)	50 (18%)
Partial response	64 (23%)	80 (29%)
Stable disease	16 (6%)	16 (6%)
Progressive disease or relapse	10 (4%)	9 (3%)
CR/CRu	184 (67%)	169 (62%)
Overall response rate	248 (91%)	249 (91%)

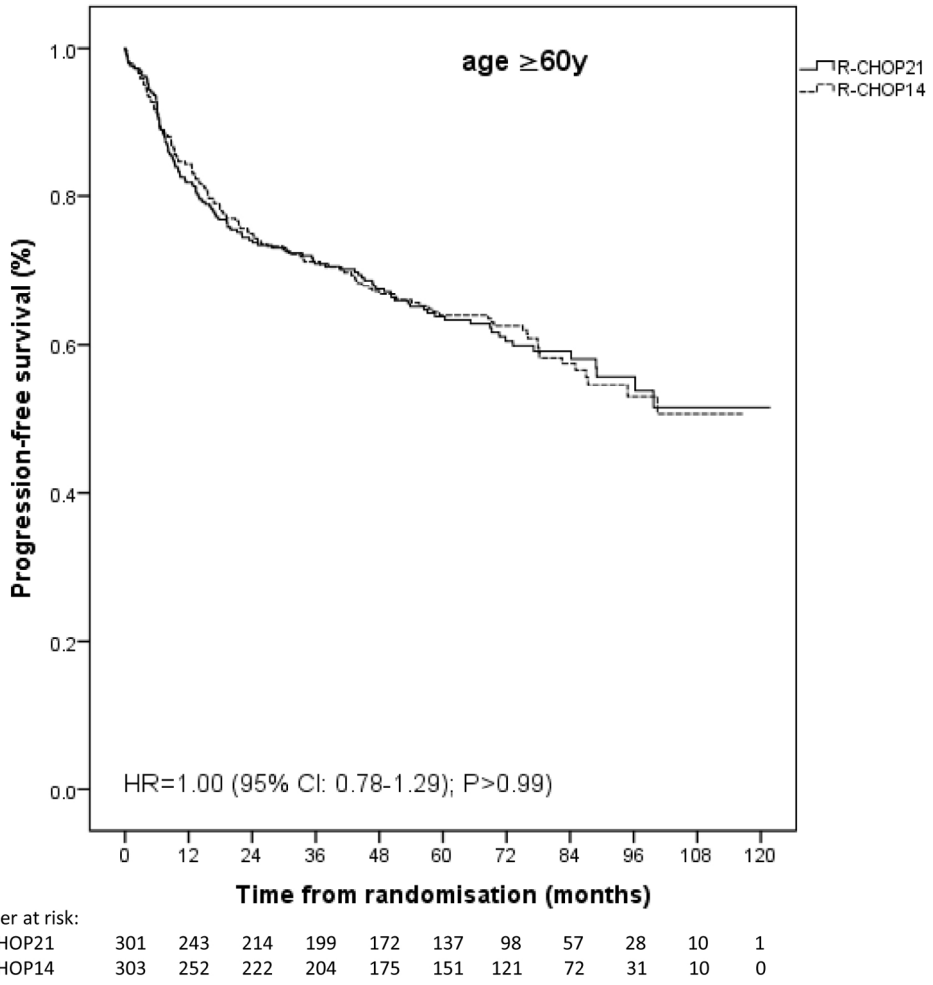

Figure 1: Kaplan-Meier curves of PFS and OS in (A) patients over 60 years and (B) patients over 70 years

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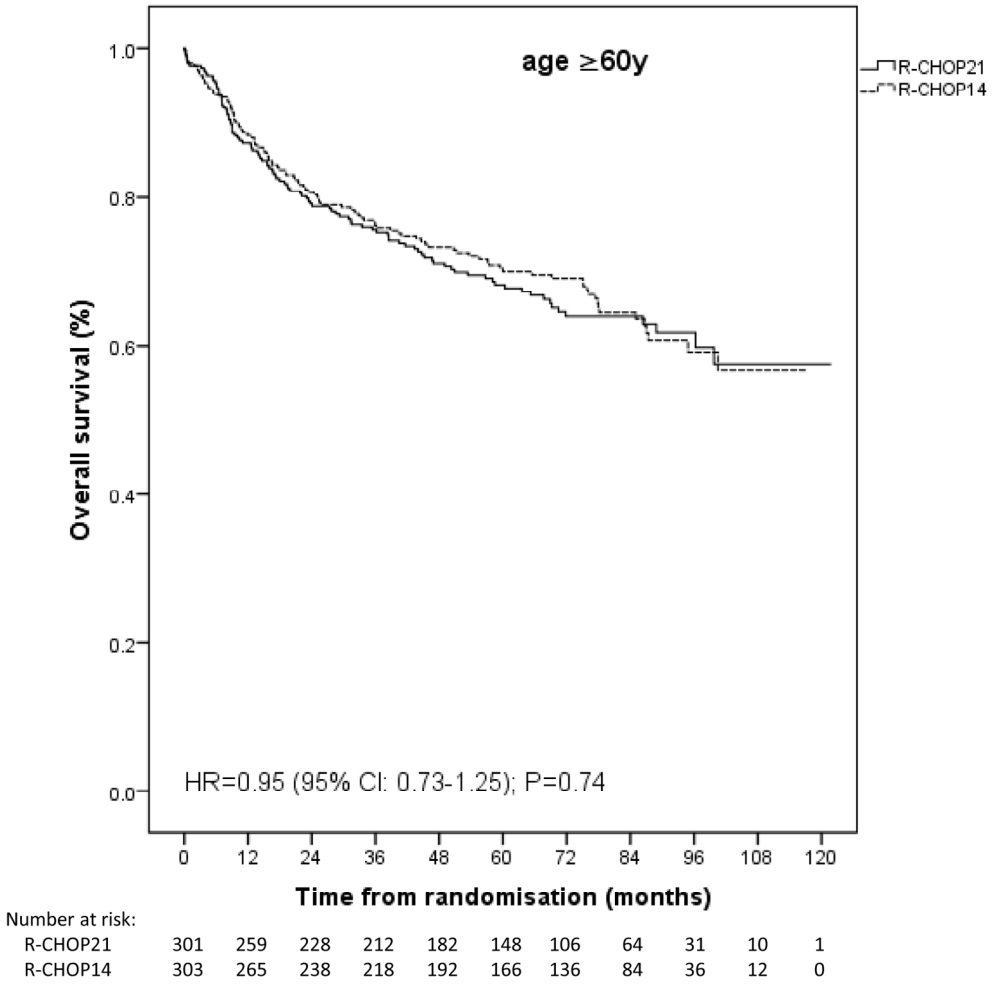

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152x152mm (300 x 300 DPI)

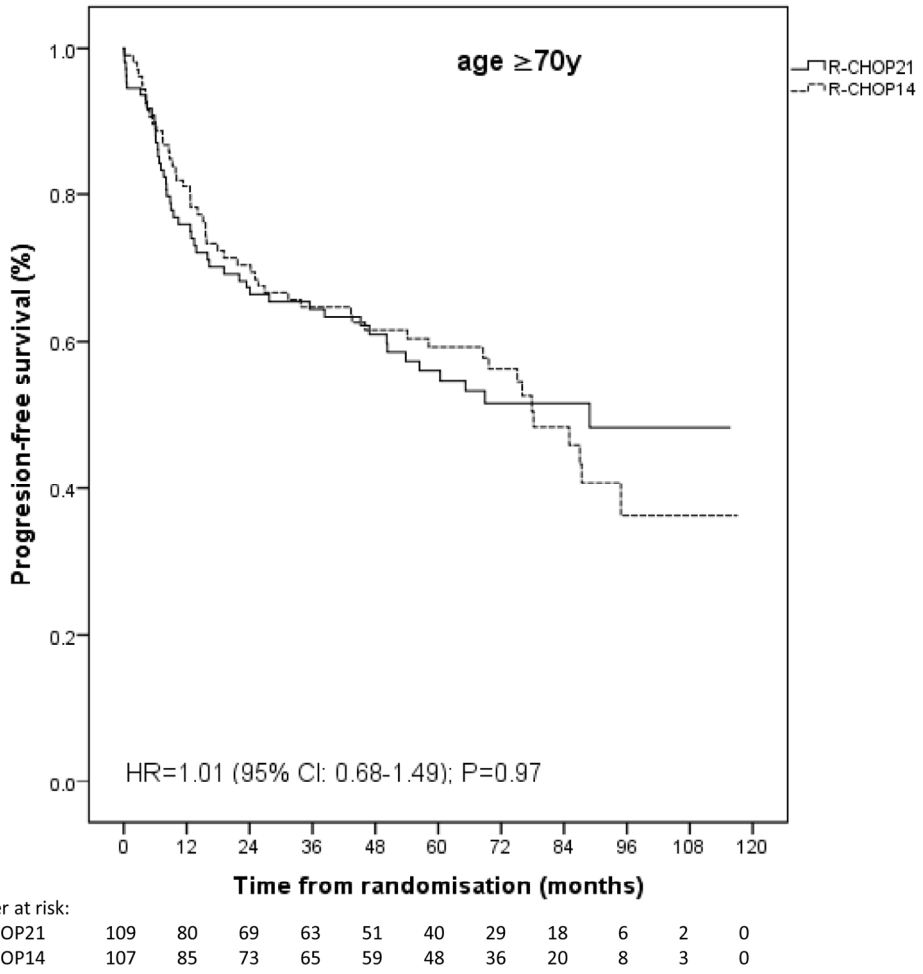


Figure 1: Kaplan-Meier curves of PFS and OS in (A) patients over 60 years and (B) patients over 70 years

154x153mm (300 x 300 DPI)

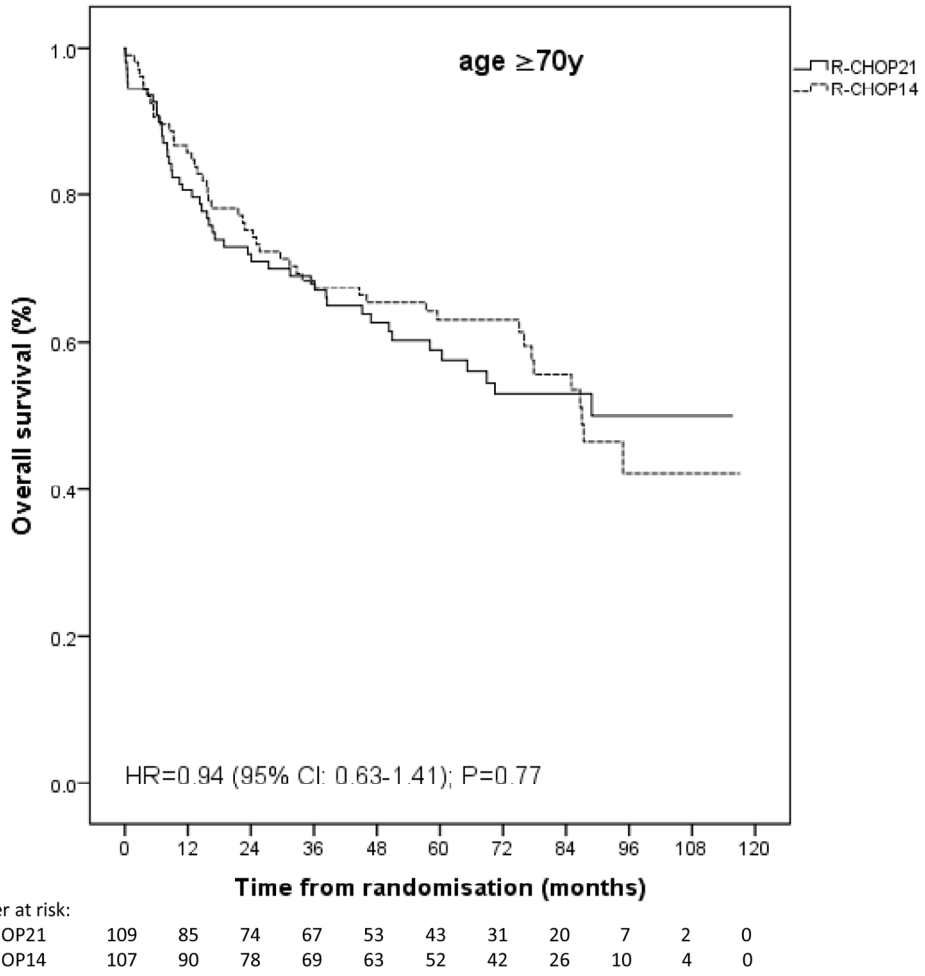
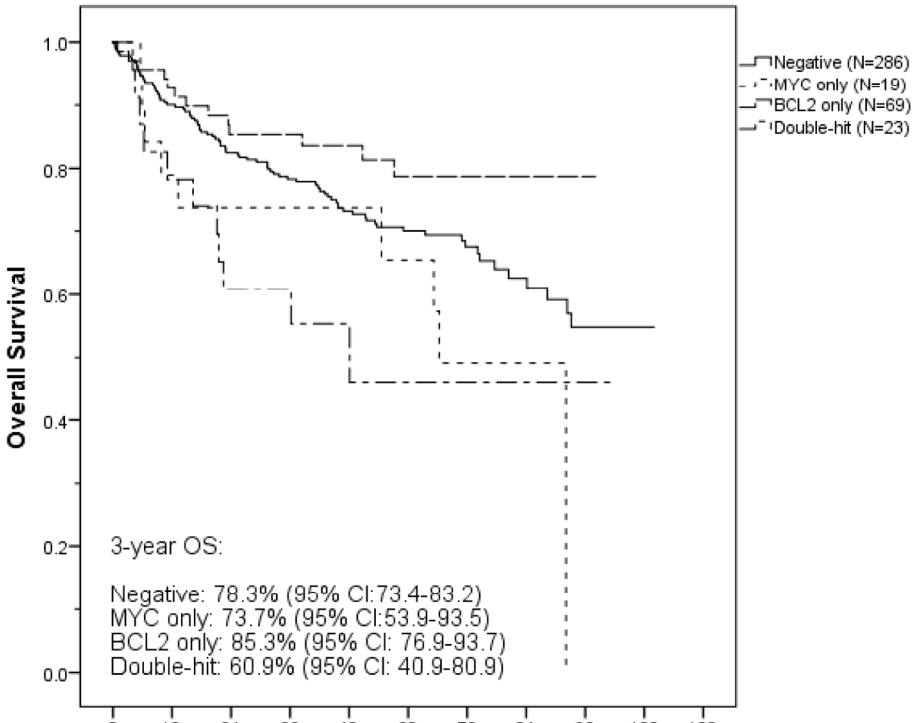


Figure 1: Kaplan-Meier curves of PFS and OS in (A) patients over 60 years and (B) patients over 70 years

154x153mm (300 x 300 DPI)



Number at risk:

Negative	286	251	227	199	159	118	71	40	17	1	0
MYC only	19	15	14	12	10	8	6	3	0	0	0
BCL2 only	69	64	57	50	41	29	16	8	1	0	0
Double-hit	23	18	14	11	6	4	1	1	1	0	0

164x150mm (300 x 300 DPI)

Supplement

Patients and Methods

In the phase 3 UK NCRI R-CHOP14v21 trial, patients aged 18 years or older with untreated stage IA bulky or stage IB-IV DLBCL were randomly assigned between 2005 and 2008 to receive either 8 cycles R-CHOP-21 or 6 cycles R-CHOP-14 (+ G-CSF) with two additional rituximab applications. Doses of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone were based on the original GELA and DSHNHL regimens. G-CSF was administered on days 4-12 of each cycle. 57% of patients in the R-CHOP-21 arm received G-CSF as secondary prophylaxis at the discretion of the investigators. All patients received antibiotic prophylaxis with co-trimoxazole until 2 weeks after the end of treatment. Performance of consolidation radiotherapy was at the discretion of the investigators. Response assessment was performed using contrast-enhanced CT scans after 4 cycles of therapy, at the end of treatment, and 3 months and 12 months after completion of treatment. Histological diagnosis was confirmed in central histopathology review including immunohistochemistry (IHC)-based cell-of-origin classification using the Hans algorithm. The R-CHOP14v21 trial was conducted according to the Declaration of Helsinki and all participants provided written informed consent.

604 patients in the R-CHOP14v21 trial were ≥60 years and included in the current subgroup analysis (301 in the R-CHOP-21 arm, 303 in the R-CHOP-14 arm). The median follow-up was 77.7 months.

For the joint analysis of *MYC*-R and DHL in elderly DLBCL patients, molecular data was available for 215 R-CHOP14v21 cases and 182 R-CHOP-treated patients from RICOVER-60. Patients in the combined cohorts with available molecular data were more frequently female (52% vs. 46%; P=0.05), had fewer WHO performance status 2 (11% vs. 17%; P=0.01), fewer bulky disease (33% vs. 45%; P<0.01) and fewer B symptoms (32% vs. 40%; P=0.01) compared to patients without molecular data. Molecular results were not blinded for outcome analyses.

Statistics

The primary endpoint of the R-CHOP14v21 trial was overall survival (OS). Secondary outcome measures were response rate, progression-free survival (PFS) and toxicity.

Response was assessed by the local treating physician and categorised into complete response (CR), unconfirmed CR (CRu), partial response (PR), stable disease (SD) and progressive disease (PD) in accordance with the International Workshop Standardized

Response Criteria for Non-Hodgkin Lymphoma. Adverse events were classified using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0). Patients who received at least one cycle of therapy were included in the toxicity analyses.

OS and PFS were calculated by the Kaplan-Meier method with the log-rank comparing differences between survival curves. Clinical findings were compared between groups using the $\chi 2$ or Mann-Whitney U test. A *P* value of ≤ 0.05 (two-sided) was regarded as significant. Multivariate analyses were performed using Cox logistic regression including the following variables: age as continuous variable, WHO performance status (PS) 0/1 vs. ≥ 2, LDH normal vs. >upper limit of normal (ULN), Stage I/II vs. III/IV, number of extranodal sites involved 0-1 vs. ≥ 2, gender, bulky disease (diameter >10cm) absent vs. present, $\beta 2$-microglobulin (B2M) <3mg/L vs. ≥3mg/L, and albumin >35 g/L vs. ≤35 g/L.

The age-specific prognostic scores elderly IPI (E-IPI) and ABE4 were compared with standard IPI and revised IPI (R-IPI). In contrast to the original publication, bulky disease was defined as tumour of greater than 10cm (not 7.5cm) to calculate the ABE4 score. Performance of scores were compared by global fit criterion AIC (Akaike's information criteria) and discrimination according to CPE (concordance probability estimate), with lower values of AIC indicating better fit and higher values of CPE better discrimination

Supplementary Tables and Figures

Table S1: Clinical characteristics according to MYC-R and DHL

Characteristics	**non-MYC (*N*=379)** *n* (%)	**MYC-R (*N*=42)** *n* (%)	**non-DHL (*N*=374)** *n* (%)	**DHL (*N*=23)** *n* (%)
Age (years)				
60-69	233 (61%)	25 (60%)	230 (61%)	14 (61%)
≥70	146 (39%)	17 (40%)	144 (39%)	9 (39%)
Sex				
Female	197 (52%)	18 (43%)	196 (52%)	11 (48%)
Male	182 (48%)	24 (57%)	178 (48%)	12 (52%)
Stage III/IV	203 (54%)	19 (45%)	201 (54%)	13 (57%)
WHO performance status >1	40 (11%)	7 (17%)	39 (10%)	4 (17%)
Elevated LDH	201 (53%)	26 (62%)	205 (55%)	15 (65%)
>1 extranodal sites	83 (22%)	9 (21%)	80 (21%)	7 (30%)
IPI score				
1	110 (29%)	13 (31%)	105 (28%)	5 (22%)
2	93 (25%)	10 (24%)	95 (25%)	5 (22%)
3	110 (29%)	10 (24%)	110 (29%)	7 (30%)
4	57 (15%)	6 (14%)	54 (14%)	4 (17%)
5	9 (2%)	3 (7%)	10 (3%)	2 (9%)
Bulk	118 (31%)	19 (45%)	121 (32%)	11 (48%)
B symptoms	120 (32%)	17 (40%)	118 (32%)	9 (39%)

Table S2: Reasons for early termination of treatment

Reason for early termination	R-CHOP-21 (*N*=301) *n*	R-CHOP-14 (*N*=303) *n*
Disease progression (PD)	7	4
-Death due to PD	1	2
Clinical decision	8	1
Patient refusal	6	5
Other medical condition	10	9
-Death due to other medical condition	3	3
Treatment-related toxicity	27	19
-Death related to treatment	3	7
Death, other cause or unknown	2	1
Diagnosis changed	3	4
Other	7	2
Not known/missing	1	1

Table S3: Survival status and cause of death

Status and cause of death	R-CHOP-21 (*N*=301) *n* (%)	R-CHOP-14 (*N*=303) *n* (%)
Alive without progression	184 (61%)	182 (60%)
Alive after progression	14 (5%)	18 (6%)
Dead	103 (34%)	103 (34%)
Non-Hodgkin Lymphoma	58	52
Treatment related toxicity	3	7
Secondary Malignancy	10	11
Cardiac Death	6	7
Other	26	22
Missing	0	4

Table S4: Overall survival

Variable	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
R-CHOP-14 arm	0.95 (0.73-1.25)	0.74	1.11 (0.78-1.60)	0.55
Age (per year)	1.07 (1.05-1.09)	<0.0001	1.05 (1.02-1.08)	<0.01
Stage III/IV	1.30 (0.97-1.76)	0.08	1.25 (0.82-1.89)	0.30
PS >1	1.51 (1.08-2.13)	0.02	1.01 (0.63-1.64)	0.96
LDH >ULN	1.60 (1.17-2.18)	<0.01	1.37 (0.89-2.11)	0.15
Extranodal sites >1	1.33 (1.00-1.77)	0.05	1.01 (0.68-1.50)	0.96
B2M ≥3mg/L	2.15 (1.48-3.12)	<0.0001	1.54 (1.02-2.33)	0.04
Bulky disease	1.08 (0.82-1.43)	0.57	0.98 (0.67-1.43)	0.92
Male sex	1.13 (0.86-1.48)	0.39	1.03 (0.72-1.47)	0.88
Albumin ≤35g/L	1.79 (1.35-2.36)	<0.0001	1.43 (0.97-2.12)	0.07

Table S5: Performance of prognostic scores

Groups (no. of factors)	Patients *n* (%)	CPE	AIC
IPI (age ≥60y, WHO PS >1, Stage III/IV, LDH >ULN*, extranodal sites >1)			
Low (0-1)	92 (15)		
Low-intermediate (2)	165 (27)	0.571	2486
High-intermediate (3)	202 (33)		
High (4-5)	145 (24)		
R-IPI (age ≥60y, WHO PS >1, Stage III/IV, LDH >ULN, extranodal sites >1)			
Very good (0)	0 (0)		
Good (1-2)	257 (43)	0.558	2488
Poor (3-5)	347 (57)		
E-IPI (age ≥70y, WHO PS >1, Stage III/IV, LDH >ULN, extranodal sites >1)			
Low (0-1)	150 (25)		
Low-intermediate (2)	180 (30)	0.546	2494
High-intermediate (3)	175 (29)		
High (4-5)	99 (16)		
ABE4 (age ≥70y, WHO PS ≥1, bulky disease)			
Low (0)	114 (19)		
Low-intermediate (1)	215 (36)	0.593	2479
High-intermediate (2)	218 (36)		
High (3)	57 (9)		

*ULN indicates upper limit of normal.

Figure S1: Kaplan-Meier curves of PFS and OS according to COO subtypes

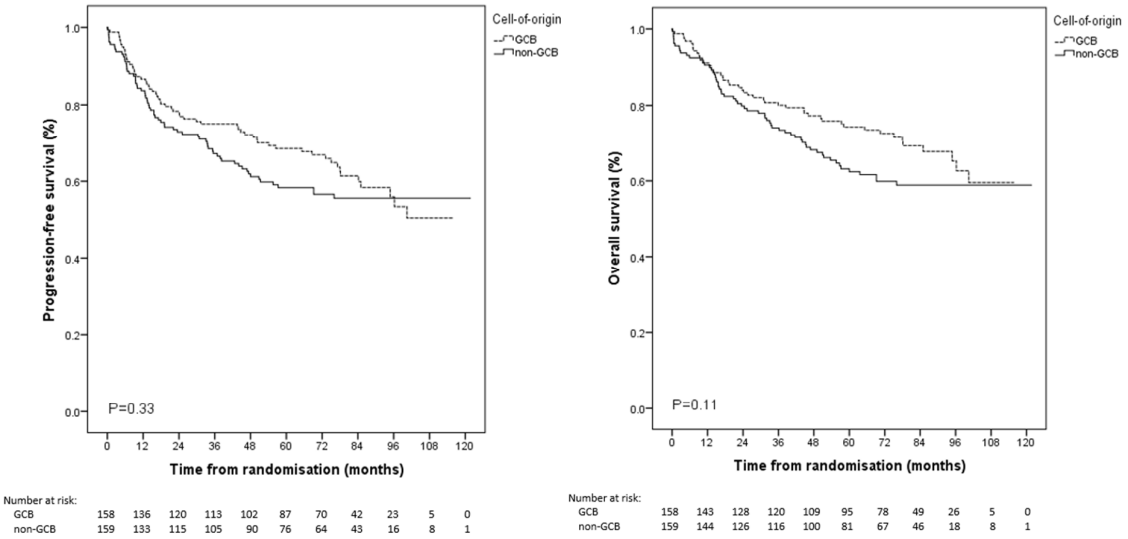
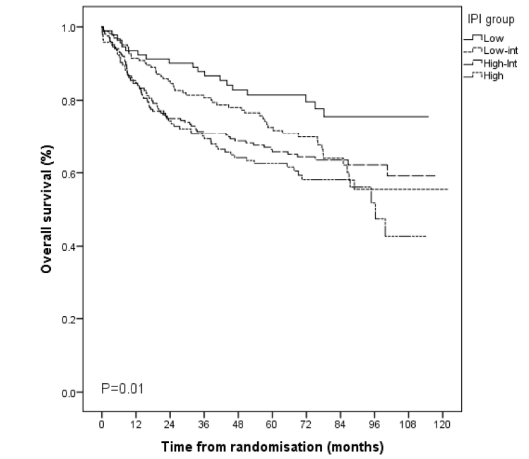
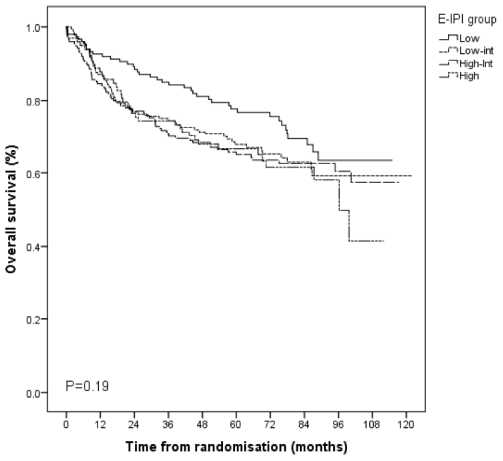


Figure S2: Kaplan-Meier curves of OS according to different prognostic scores



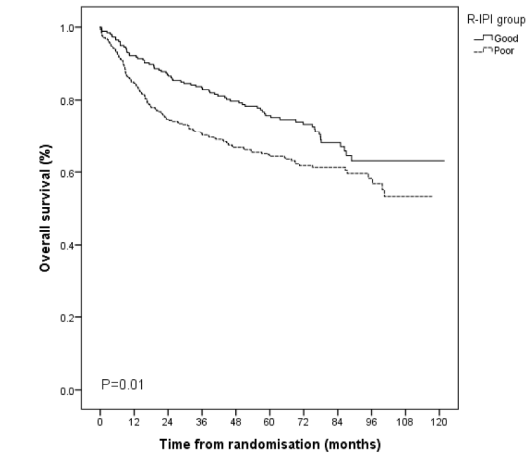
Number at risk:

Low	92	84	79	75	62	54	43	30	13	2	0
Low-int.	165	149	134	122	106	87	68	36	13	3	1
High-int.	202	169	147	136	123	105	85	53	29	14	0
High	145	122	106	97	83	68	46	29	12	3	0



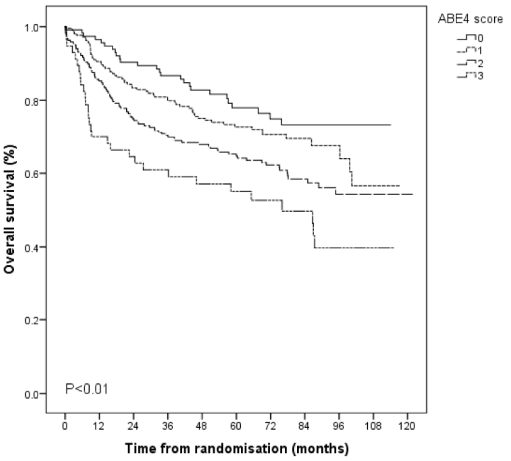
Number at risk:

Low	150	136	127	118	100	85	67	42	16	2	0
Low-int.	180	154	133	123	106	87	71	40	17	8	1
High-int.	175	148	132	119	110	96	71	47	27	10	0
High	99	86	74	70	58	46	33	19	7	2	0



Number at risk:

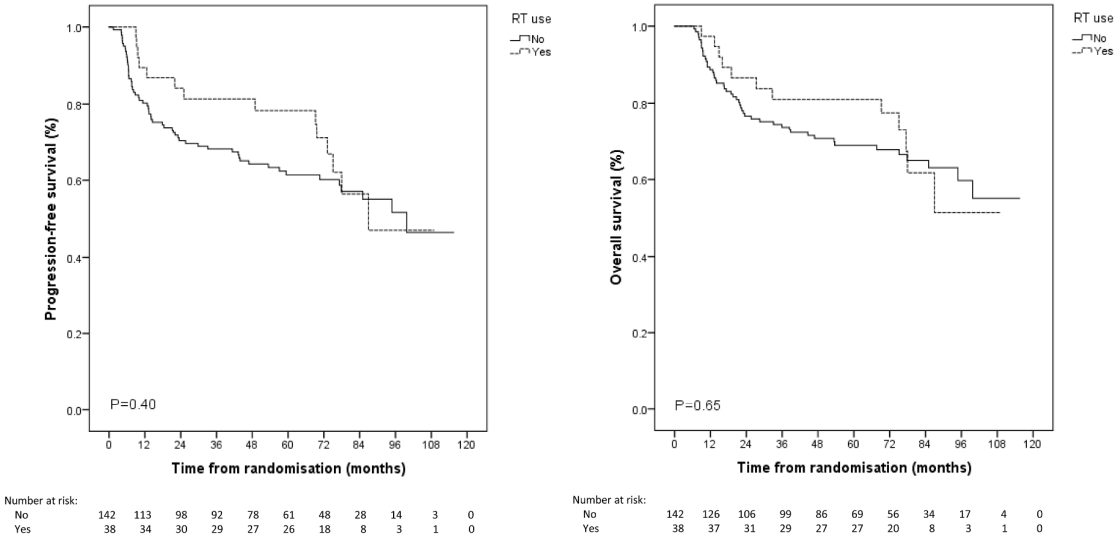
Good	257	233	213	197	168	141	111	66	26	5	1
Poor	347	291	253	233	206	173	131	82	41	17	0



Number at risk:

0	114	110	101	94	77	61	49	30	13	4	0
1	215	191	170	157	137	111	81	46	21	6	0
2	218	184	159	147	132	116	92	57	27	8	1
3	57	39	36	32	28	26	20	15	6	4	0

Figure S3: Kaplan-Meier curves of PFS and OS according to consolidation radiotherapy (RT) in patients with PR or SD at the end of chemotherapy



Number at risk:

No	142	113	98	92	78	61	48	28	14	3	0
Yes	38	34	30	29	27	26	18	8	3	1	0

Number at risk:

No	142	126	106	99	86	69	56	34	17	4	0
Yes	38	37	31	29	27	27	20	8	3	1	0

Table S1: Clinical characteristics according to MYC-R and DHL

Characteristics	non-MYC (*N*=379) *n* (%)	MYC-R (*N*=42) *n* (%)	non-DHL (*N*=374) *n* (%)	DHL (*N*=23) *n* (%)
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Secondary Malignancy	10	11
Cardiac Death	6	7
Other	26	22
Missing	0	4

Table S4: Overall survival

Variable	Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*
R-CHOP-14 arm	0.95 (0.73-1.25)	0.74	1.11 (0.78-1.60)	0.55
Age (per year)	1.07 (1.05-1.09)	<0.0001	1.05 (1.02-1.08)	<0.01
Stage III/IV	1.30 (0.97-1.76)	0.08	1.25 (0.82-1.89)	0.30
PS >1	1.51 (1.08-2.13)	0.02	1.01 (0.63-1.64)	0.96
LDH >ULN	1.60 (1.17-2.18)	<0.01	1.37 (0.89-2.11)	0.15
Extranodal sites >1	1.33 (1.00-1.77)	0.05	1.01 (0.68-1.50)	0.96
B2M ≥3mg/L	2.15 (1.48-3.12)	<0.0001	1.54 (1.02-2.33)	0.04
Bulky disease	1.08 (0.82-1.43)	0.57	0.98 (0.67-1.43)	0.92
Male sex	1.13 (0.86-1.48)	0.39	1.03 (0.72-1.47)	0.88
Albumin ≤35g/L	1.79 (1.35-2.36)	<0.0001	1.43 (0.97-2.12)	0.07

Table S5: Performance of prognostic scores

Groups (no. of factors)	Patients *n* (%)	CPE	AIC
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Low (0-1)	92 (15)		
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High (4-5)	145 (24)		
R-IPI (age ≥60y, WHO PS >1, Stage III/IV, LDH >ULN, extranodal sites >1)			
Very good (0)	0 (0)		
Good (1-2)	257 (43)	0.558	2488
Poor (3-5)	347 (57)		
E-IPI (age ≥70y, WHO PS >1, Stage III/IV, LDH >ULN, extranodal sites >1)			
Low (0-1)	150 (25)		
Low-intermediate (2)	180 (30)	0.546	2494
High-intermediate (3)	175 (29)		
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ABE4 (age ≥70y, WHO PS ≥1, bulky disease)			
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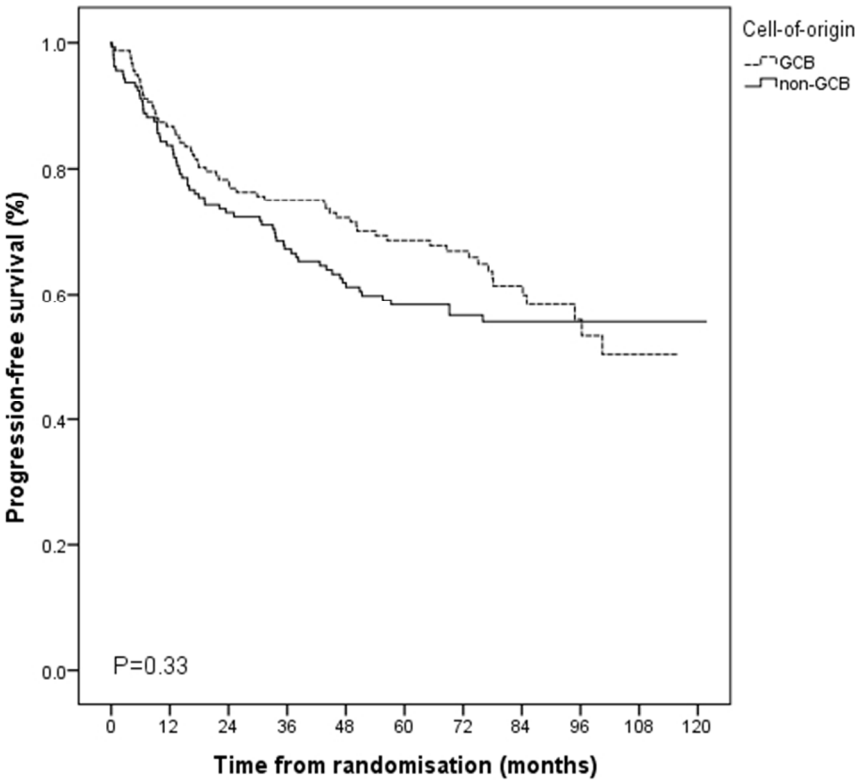
*ULN indicates upper limit of normal.



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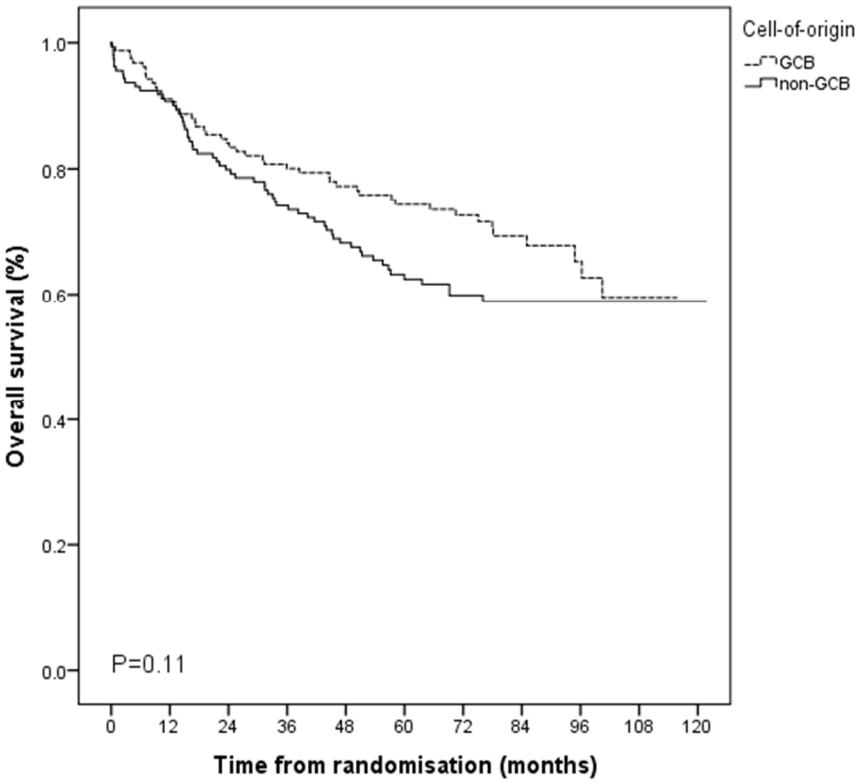

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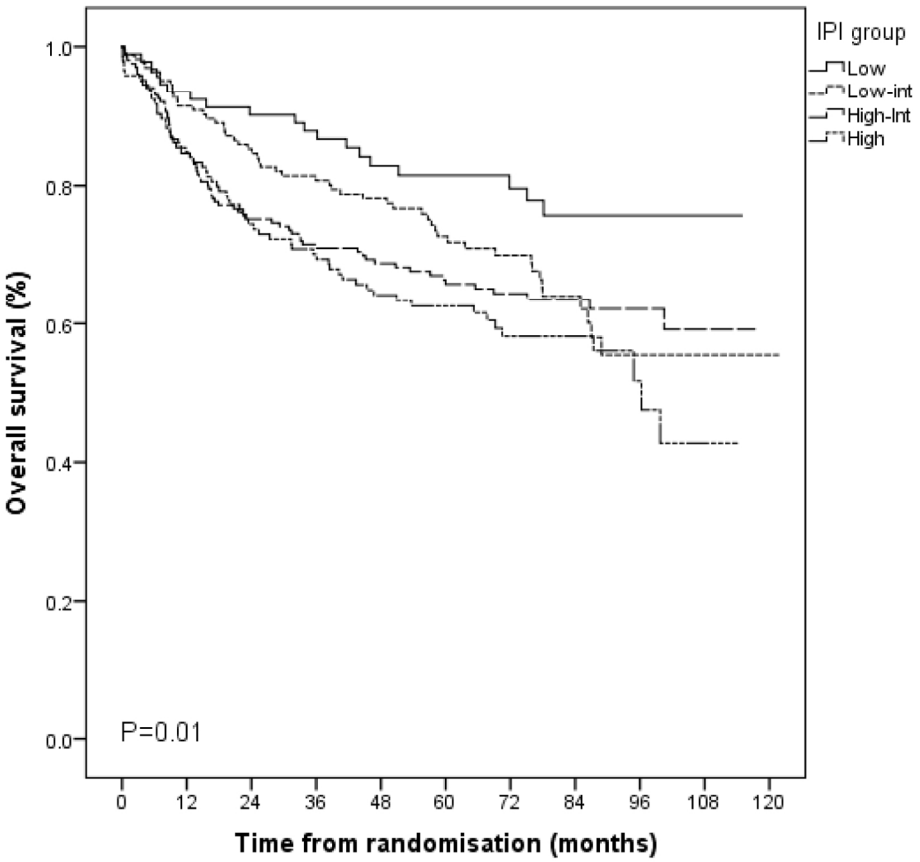

Number at risk:

Low	92	84	79	75	62	54	43	30	13	2	0
Low-int.	165	149	134	122	106	87	68	36	13	3	1
High-int.	202	169	147	136	123	105	85	53	29	14	0
High	145	122	106	97	83	68	46	29	12	3	0

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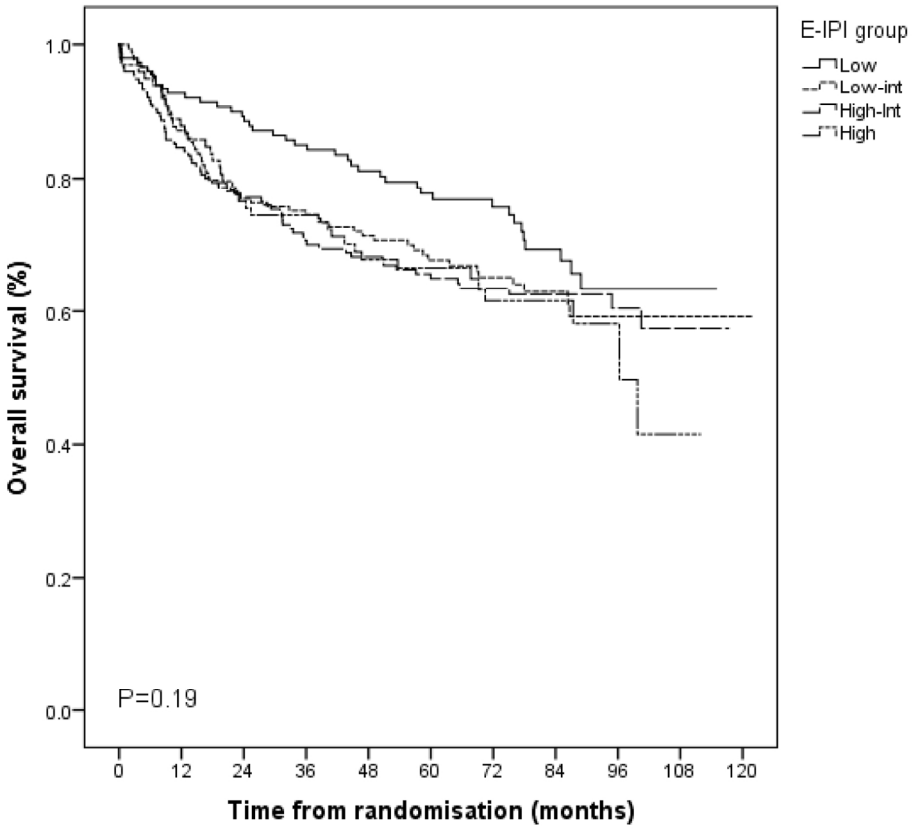
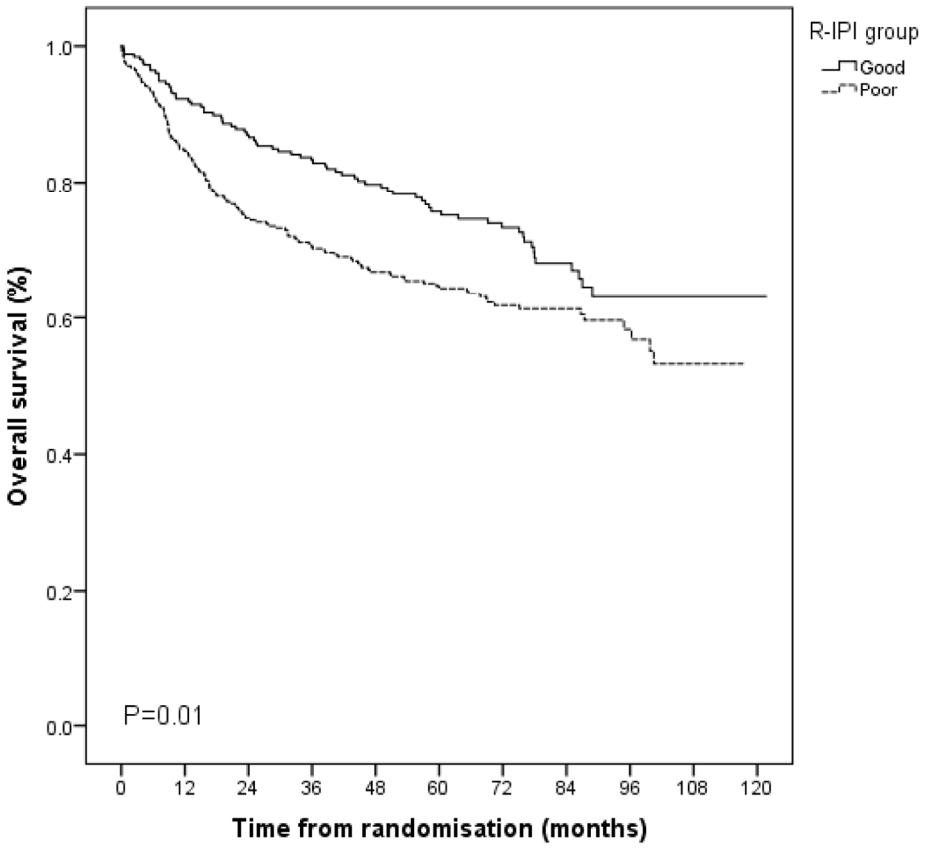


Number at risk:

Low	150	136	127	118	100	85	67	42	16	2	0
Low-int.	180	154	133	123	106	87	71	40	17	8	1
High-int.	175	148	132	119	110	96	71	47	27	10	0
High	99	86	74	70	58	46	33	19	7	2	0

156x156mm (300 x 300 DPI)



Number at risk:

Good	257	233	213	197	168	141	111	66	26	5	1
Poor	347	291	253	233	206	173	131	82	41	17	0

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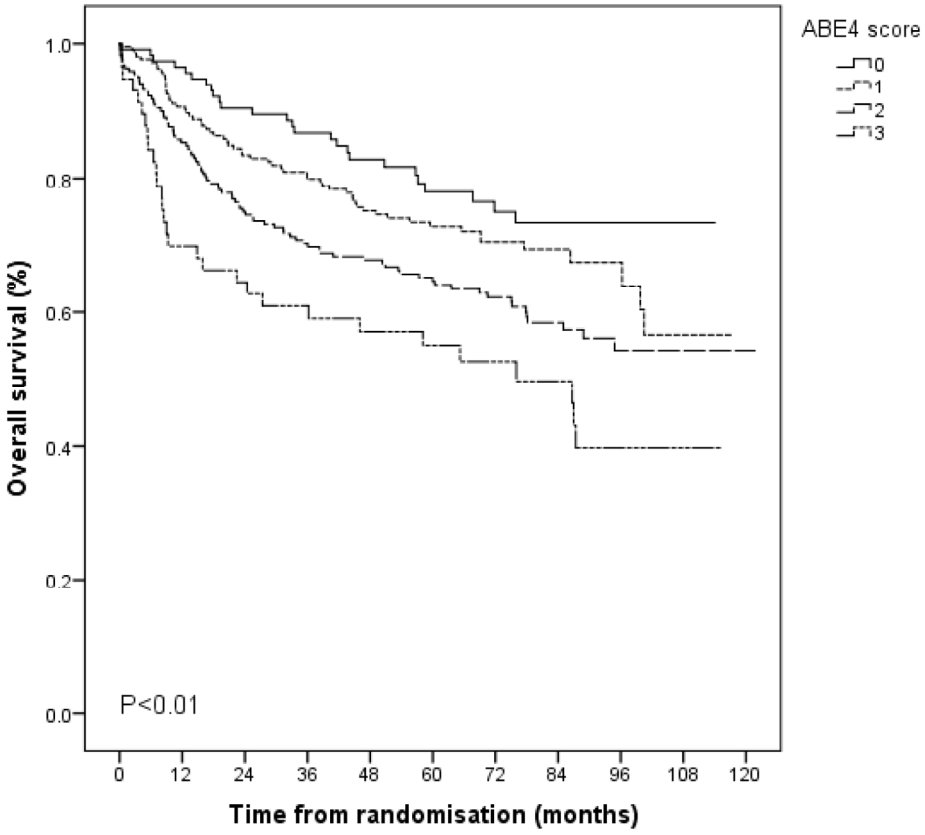
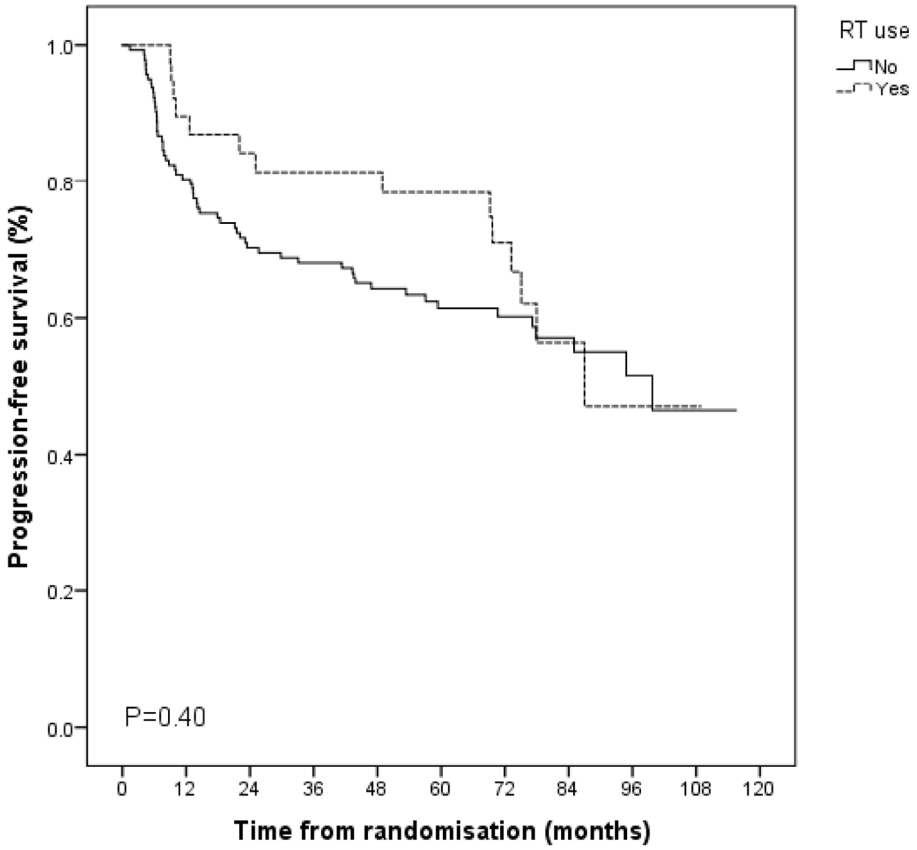


Number at risk:

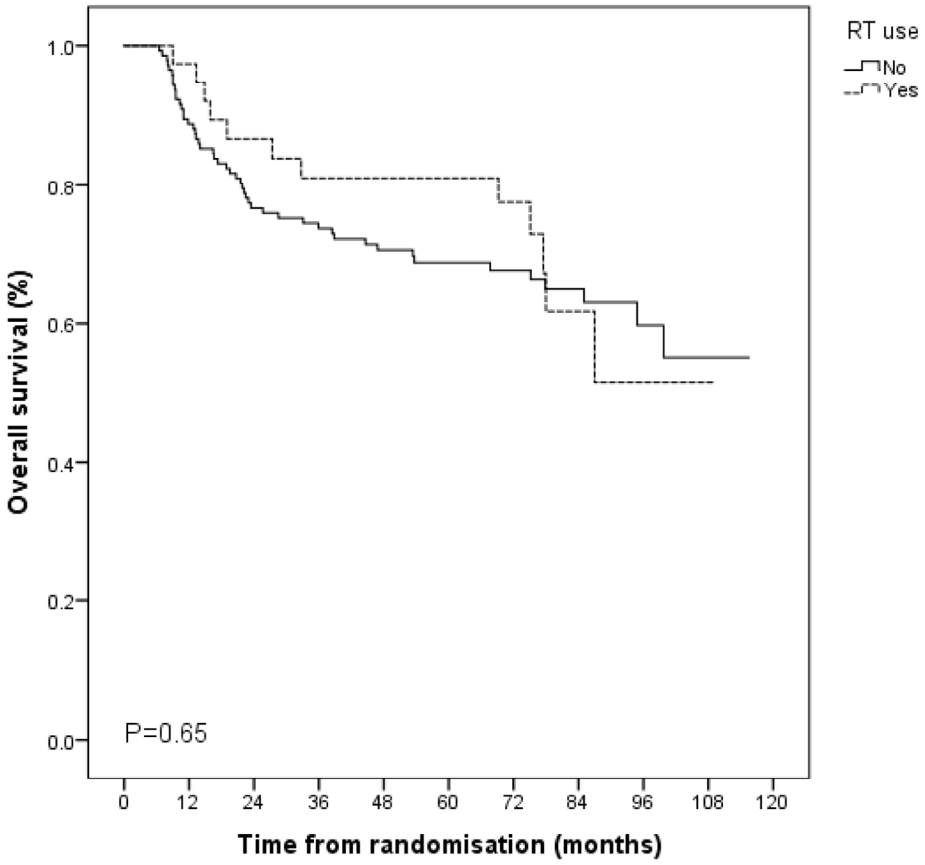
0	114	110	101	94	77	61	49	30	13	4	0
1	215	191	170	157	137	111	81	46	21	6	0
2	218	184	159	147	132	116	92	57	27	8	1
3	57	39	36	32	28	26	20	15	6	4	0

155x155mm (300 x 300 DPI)



Number at risk:											
No	142	113	98	92	78	61	48	28	14	3	0
Yes	38	34	30	29	27	26	18	8	3	1	0

152x148mm (300 x 300 DPI)



Number at risk:

No	142	126	106	99	86	69	56	34	17	4	0
Yes	38	37	31	29	27	27	20	8	3	1	0

149x148mm (300 x 300 DPI)